REMARKS

Claims 1, 3, 5 and 11-14 are pending. Claims 2, 4, 6-10 and 15-18 are canceled. Claims 1 and 11 are amended. Claims 19-25 are added. No new matter is added.

The claims have been amended to address the treatment of Celiac sprue (Claims 1, 3-5, 11-14, and 23-25) separately from the treatment of dermatitis herpetiformis (Claims 19-22). Newly added Claims 20 and 23 specifically recited the elected compound[(S)-1-[(3-Bromo-4,5-dihydro-isoxazol-5-ylmethyl)-methyl-carbamoyl]-2-(4-hydroxy-phenyl)-ethyl]-carbamic acid benzyl ester (see the Applicants' request for a change of elected species below).

Paragraph 60 is amended herewith to correct an obvious typographical error.

Claims 1, 3-5 and 11-14 have been rejected under 35 U.S.C. 103. Applicants respectfully request the Examiner to allow the Applicants to change the elected species and to reconsider and withdraw the original restriction requirement with respect to searching the genus defined by Claims 1 and 11 as well as the rejection under 35 U.S.C. 103.

RESTRICTION ELECTION – CHANGE REQUESTED

In Applicants' restriction election of May 31, 2006, the molecule {(S)-1-[(3-Bromo-4,5-dihydro-isoxazol-5-ylmethyl)-carbamoyl]-2-phenyl-ethyl}-carbamic acid benzyl ester was elected for examination, with traverse. As discussed with the Examiner, Applicants request a change in this election, also with traverse, to the molecule [(S)-1-[(3-Bromo-4,5-dihydro-isoxazol-5-ylmethyl)-methyl-carbamoyl]-2-(4-hydroxy-phenyl)-ethyl]-carbamic acid benzyl ester, which differs from the originally elected invention in the underlined 4-hydroxy moiety. This change is requested, because Applicants intended to elect this molecule, but due to a miscommunication, erroneously elected the structurally related molecule. Applicants regret the inconvenience caused Examiner by this requested change of election. Newly added Claim 20 is specifically drawn to a method of treating Celiac sprue with this newly elected molecule. The Applicants hope that any inconvenience to the Examiner of allowing this change is greatly reduced due to the fact that both the previously elected and newly elected compounds are disclosed in the cited references Castelhano *et al.* US Patent nos. 4,929,630 and 4,912,120. It is hoped that the requested change of election can be granted without undue burden on the Examiner. As discussed below, Applicants respectfully submit that the presently claimed methods are not taught in the cited art.

The Applicants also request the Examiner to reconsider the decision not to search the Claims drawn to a genus comprising the elected species. The Office Action states, with respect to

the previous restriction requirement, that isoxazole is not a novel compound, and that no substantial novel core exists among the genus formula/compound that would allow for a coextensive search of said compounds in the present methods of use. Applicants respectfully submit that the present claims are properly searched for methods having the full scope of the generic formula set forth in Claims 1 and 11 (and new Claim 19).

Applicants are unaware of any requirement for a substantial novel core in compounds where the claims are drawn to methods of use, and not to the compounds themselves. The present claims are directed to method of treating Celiac sprue or dermatitis herpetiformis with a recited class of compounds. While not all of the compounds in the genus are novel, the method of treatment with the compounds are novel.

Applicants further submit that the generic formula set forth in the present claims provides a common structural core for searching. As set forth in the TC1600 Restriction Training for Examiners (August 2004), Example 2, claims for a method of treatment are grouped in a single invention *even when the claims recite a generic structure for the compound*. The compounds defined in the claims of the present invention have similar structure and a common core (the isoxazole moiety).

As discussed in MPEP 806.04(a), species may be related under the particular disclosure. Where inventions as disclosed and claimed are both (A) species within a claimed genus and (B) related, then the question of restriction must be determined by both the practice applicable to election of species and the practice applicable to other types of restrictions, such as those covered in MPEP § 806.05 - § 806.05(i).

In general, a generic claim should include no material element additional to those recited in the species claims, and must comprehend within its confines each of the species. For the purpose of obtaining claims to more than one species in the same case, the generic claim cannot include limitations not present in each of the added species claims. Otherwise stated, the claims to the species that can be included in an application in addition to a single species must contain all the limitations of the generic claim.

A key determination in whether a generic claim is appropriate is whether the disclosure recites a commonality of operation, function, or effect. In the methods of the present invention, each of these conditions is met.

With respect to operation and function, the claimed genus defines a specific functional group, *i.e.* a dihydroisoxazole, common to all compounds defined by the generic structure in the genus claim. For example, Claim 1 recites a method in which compounds defined by a generic formula comprising a 3-halo-4,5-dihydroisoxazole moiety are used to treat Celiac sprue. This functional group provides for the operation and function of the compounds as tissue

transglutaminase inhibitors, and thus, there is a commonality of operation and function in the genus. Further, the present claims relate to a method of treatment, wherein the dihydroisoxazole compound attenuates gluten toxicity in said patient, thus providing for a common effect within the genus.

Applicants respectfully submit that that the generic methods as set forth in Claims 1,11, and 19 are properly examined as a group, with a species election of the specific compound, [(S)-1-[(3-Bromo-4,5-dihydro-isoxazol-5-ylmethyl)-methyl-carbamoyl]-2-(4-hydroxy-phenyl)-ethyl]-carbamic acid benzyl ester, and respectfully request reconsideration of the requirement.

In the event that the Examiner does not rejoin the generic group, the Applicants respectfully traverse the restriction for the reasons stated above, and reserve the right under 37 CFR 1.144 to petition the Director to review the requirement. The Applicants understand that petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal.

Claims 1, 3-5 and 11-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over either Castelhano *et al.*, US 4,912,120, or Castelhano *et al.*, US 4,929,630 ("Castelhano") in view of Piper *et al.*, Biochemistry 2002 Jan 8:41(1):386-393 ("Piper).

Applicants respectfully submit that the presently claimed invention would not have been made obvious at the time the invention was made by the cited combination of references. The presently pending claims have been amended without prejudice to recite a method that involves oral administration of the transglutaminase inhibitor, as supported in originally filed Claim 4. Castelhano describes a 4,5-dihydroisoxazole as an inhibitor of bovine epidermal transglutaminase and recites the use of such compounds for diseases of the skin, specifically acne, psoriasis and cataracts.

Castelhano (columns 19-20 of either patent) recites that the compounds are useful for treating mammals, particularly humans:

> which have a disease state characterized by elevated transglutaminase activity. Such disease states are exemplified by acne, psoriasis and cataracts. For the treatment of acne, the preferred manner of administration is topically using a convenient dosage form which can be readily applied to skin and will maintain the active compounds there until beneficial action can occur. . . . When the compound is desired to diminish the conditions of cataracts, it may be administered topically directly to the eye in the form of drops of sterile, buffered ophthalmic solutions of pH 7.2-7.8.

This discussion of topical use of the transglutaminase inhibitor compounds for the treatment of certain skin and eye conditions does not teach or suggest the oral administration of such compounds to treat Celiac sprue or dermatitis herpetiformis much less that such compounds can be

enterically coated for delivery to the small intestine. It is respectfully submitted that there accordingly was no basis for rejecting the dependent claims drawn to oral administration and the method as practiced with an enteric formulation over Castelhano, alone or in combination with Piper. To expedite allowance of claims drawn to important subject matter, all of the independent claims have been amended without prejudice to recite that the compounds are orally administered, as supported in the specification and original Claim 4.

Castelhano also fails to teach that the transglutaminase inhibitor compounds describe therein could inhibit *human tissue* transglutaminase, also referred to herein as tTGase or TG2. Transglutaminases belong to a family of enzymes that play important roles in diverse biological functions by selectively cross-linking proteins. Among the members of this family are plasma transglutaminase, also known as factor XIIIa, which stabilizes fibrin clots; epidermal transglutaminase, which cross-links a range of differentiation-specific structural proteins, such as involucrin, loricrin, filaggrin, and small proline-rich proteins, in the formation of the cornified cell envelope in the biogenesis of the stratum corneum, the outermost, "dead" layer of the epidermis; and tissue transglutaminase, which cross-links fibronectin in the extracellular matrix of organs such as brain, liver and the intestine. .

The different transglutaminases vary in their substrate specificity and in their inhibition profile. For a review, see the attached Greenberg *et al.* (1991) article. In particular, the epidermal transglutaminase (TG3) has a different activity profile than TG2. For example, Hitomi *et al.* (2000) Biosci Biotechnol Biochem. 64(3):657-9 (attached), teaches that GTP, an inhibitor of transglutaminases, is hydrolyzed by TG2 but not by TG3.

One of skill in the art would not be motivated to combine a reference teaching inhibition of epidermal transglutaminase (TG3) with a reference relating to Celiac sprue, because the transglutaminase involved in Celiac sprue is tissue transglutaminase (TG2). The attached articles from the laboratory of one of the present inventors discuss tissue transglutaminase in celiac disease and gluten sensitivity: Sollid and Khosla, Nat Clin Pract Gastroenterol Hepatol. 2005; Choi *et al.*, Chem Biol. 2005 Apr;12(4):469-75; Qiao *et al.*, J Immunol. 2005 Feb 1;174(3):1657-63.

There is no basis in Castelhano for concluding that, at the time of the present invention, an ordinarily skilled artisan would have predicted that the epidermal bovine-TGase-identified compounds identified therein would inhibit human TG2, or would be effective in the treatment of Celiac sprue or dermatitis herpetiformis or that such compounds could be orally administered to treat such conditions.

Castelhano, as the Examiner recognizes, does not discuss Celiac sprue or dermatitis herpetiformis, and Piper, the other reference cited by the Examiner, does not discuss TG3 as having any causative role in these indications. Accordingly, the Applicants submit that only impermissible hindsight reconstruction of the invention provides any basis for combining these references in the context of the present application. Applicants have identified and attached herewith the reference Sardy *et al.* (2002) J. Exp. Med. 195:747-757 (hereinafter "Sardy"), for the Examiner's consideration, as it, unlike Castelhano and Piper, actually relates to TG3 (called "TGe" in Sardy) in Celiac sprue and dermatitis herpetiformis. Sardy, at page 756, first full paragraph, discusses anti-TG3 autoantibodies that appear in patients with dermatitis herpetiformis and how they likely arise as a *secondary* effect of the production of anti-TG2 (TG2 is "TGc" in Sardy) autoantibodies:

> Our hypothesis for the etiology and pathogenesis of DH is that TGc-gluten complexes initiate an IgA autoantibody response, but fail to produce high affinity anti-TGc immunoglobulins, so resulting initially in a silent CD. These Abs cross react with TGe, but are of low avidity to it. After prolonged gliadin provocation (DH patients usually show symptoms later in life than CD patients), specific cross-reacting Ab populations develop in patients who will go on to acquire DH. These Abs have a low affinity to TGc, but extremely high affinity to TGe. (citations omitted.)

Sardy relates directly to Celiac sprue and dermatitis herpetiformis yet does not suggest that either TG2 or TG3 activity is abnormally elevated in Celiac sprue or dermatitis herpetiformis patients or that inhibitors of either would be useful in treating Celiac sprue or dermatitis herpetiformis. In fact, one of ordinary skill might presume that, as Sardy teaches that anti-TG3 antibodies arise as a secondary result of the production of anti-TG2 antibodies, inhibition of TG3 would have *no* effect on either Celiac sprue or dermatitis herpetiformis. Applicants respectfully submit that Sardy, which, unlike the Castelhano patents cited by the Examiner, actually relates to Celiac sprue and dermatitis herpetiformis, demonstrates that there was no suggestion in the art at the time the present invention was made that TG3 inhibitors would be useful in the treatment of Celiac sprue or dermatitis herpetiformis.

To emphasize the latter aspect of the invention, the treatment of dermatitis herpetiformis is now independently claimed in newly submitted Claim 19, which also recites *oral* administration of a tissue transglutaminase inhibitor. The Applicants respectfully submit that Castelhano focuses on topical or ocular administration of the TG3 inhibitors described therein and so does not suggest that a TG2 inhibitor could be administered orally to treat dermatitis herpetiformis or Celiac sprue.

The Office Action cites the combination of Piper and Castelhano as having rendered the claimed invention obvious. Applicants respectfully submit that the combined references do not make obvious the presently claimed invention. Applicants reserve the right to demonstrate that Piper

cannot be cited as prior art against the claimed invention but do not believe such a showing is necessary to overcome the rejection.

While Piper describes the results it reports as laying "the groundwork for the design of small molecule mimetics of gliadin peptides as selective inhibitors of tTGase" (Abstract; tTGase refers to TG2), it does not purport to disclose any such small molecule compounds or suggest that such compounds have already been made and tested on other enzymes of the transglutaminase family. Piper instead describes TG2 specificity assays conducted with various peptides.

Piper likewise does not suggest that TG3 inhibitors or bovine epidermal TG3 inhibitors would inhibit the human TG2 enzyme or that any isoxazole, much less the specific compound recited by the Examiner, would inhibit the human TG2 enzyme.

Piper does not teach that Celiac sprue can be treated by inhibition of TG2 or that TG2 is present in elevated levels or activity in the Celiac sprue or dermatitis herpetiformis patient, as the Examiner asserts. Instead, Piper, at p. 391, right column, recites that "a growing body of results *suggests* that this enzyme is actively involved in the pathogenesis of the disease"; that "*it has been suggested* that tTGase catalyzes deamidation of gliadin peptides, which in turn enhances their immunogenicity as defined by their ability to induce T cell proliferation;" and that *"[t]o the extent that* tTGase plays a causative role in the inflammatory process, *it may be possible to attenuate* inflammation associated with Celiac Sprue by inhibition of the enzyme." (Emphasis added.) This language does not support the Examiner's view that the reference teaches that inhibition of TG2 can treat Celiac sprue, much less that there are elevated TG2 levels that need to be inhibited to treat the disease, or that an isoxazole, much less the specific compound considered by the Examiner, could be used to inhibit human TG2. Instead, the reference, at p.391, right column, correctly characterizes its teachings as aimed at "[u]nderstanding the molecular recognition features of tTGase" by examining "the specificity of tTGase toward gliadin peptides."

The concluding paragraph of Piper makes even more clear that the reference does not purport to describe any TG2 small molecule inhibitors or teach that such compounds should be used to treat Celiac sprue by inhibiting elevated TG2 levels; instead, the reference recites that the various peptides that bound to the enzyme might "adopt defined conformations" and that "a better understanding of these three-dimensional conformational constraints should facilitate the *design* of tTGase inhibitors" and that such inhibitors "*might allow* for a definitive evaluation of *whether* tTGase activity is necessary for stimulating the autoimmune response associated with Celiac Sprue." (Emphasis added).

Piper does not suggest that such inhibitors already exist or could be identified by screening inhibitors of other, non-human members of the TGase family of proteins.

Piper does not disclose any small molecule (non-peptidic) inhibitors of tTGase and does not purport to disclose such compounds or suggest that Celiac sprue can or should be treated using them. Moreover, the reference does not suggest that bovine epidermal transglutaminase is a useful model by which to identify human TG2 inhibitors

The Applicants respectfully submit that there is no basis for combining Piper with Castelhano, because Castelhano fails to mention Celiac sprue, dermatitis herpetiformis, or human TG2, and Piper does not disclose or suggest that TG2 inhibition will treat Celiac sprue or dermatitis herpetiformis or that inhibitors of bovine epidermal TG3 will inhibit human TG2. There is no basis for concluding that the combination of these references would have, at the time the present invention was made, rendered the invention obvious to the artisan of ordinary skill in this art, because none of the references cited, alone or in combination, teach that Celiac sprue or dermatitis herpetiformis can be treated with small molecule inhibitors of human TG2 that are orally administered. Accordingly, the rejection should be withdrawn.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-258CIP.

Respectfully submitted,

Date: January 23, 2007

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